Bovine Spongiform Encephalopathy

Mad Cow Disease

Importance

Bovine spongiform encephalopathy (BSE, "mad cow disease") is a type of transmissible spongiform encephalopathy (TSE) that affects cattle. TSEs are progressive and fatal neurodegenerative diseases. There are multiple TSEs which affect different species of animals including scrapie in sheep, transmissible mink encephalopathy (TME, mink scrapie), feline spongiform encephalopathy (FSE), chronic wasting disease (CWD) in deer and elk, and a spongiform encephalopathy of exotic ruminants. These diseases were once thought to be entirely species specific, but it now appears that some agents can cross species barriers. In the United Kingdom, factors leading to the BSE epidemic may have been responsible for concurrent outbreaks of FSE in cats and spongiform encephalopathy in exotic ruminants. BSE has also been linked to a variant of Creutzfeldt-Jakob disease (CJD) in humans.

Etiology

BSE is thought to be caused by prions, a proteinaceous infectious particle that is smaller than the smallest known virus. Prions have not been completely characterized and a minority opinion is that BSE may be caused by virinos or retroviruses. The BSE agent is extremely resistant to the treatments that ordinarily destroy bacteria, spores, viruses, and fungi and can survive in tissue post-mortem.

Species affected

BSE is seen in cattle and can be experimentally transmitted to cats, mink, mice, pigs, sheep, goats, marmosets and cynomolgus monkeys.

Geographic distribution

BSE appears to have originated in the United Kingdom in 1986. Infected indigenous cattle have since been found in Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Lichtenstein, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, and Switzerland, in addition to the United Kingdom. Cases have also been seen in imported cattle in Oman, Liechtenstein, Luxembourg, and the Falkland Islands. The United States reported a single cow with BSE in 2003.

BSE has never been detected in Australia, New Zealand, Central America or South America.

Transmission

BSE seems to be transmitted orally and is thought to have mutated from the scrapie agent found in sheep. The first cases of BSE appeared in the U.K. in 1986 and have been linked to changes in the rendering practices for livestock feed. These changes may have allowed infectious meat or bone meal from scrapie-infected sheep to be fed to cattle. Rendering of contaminated cattle carcasses and wastes seems to have amplified the agent. A minority of researchers believes that BSE has always existed in cattle but was unrecognized until the outbreak in the U.K.

The BSE agent is found mainly in nervous tissues. In naturally infected cattle, it has been detected only in the brain, spinal cord, and retina. In experimentally infected calves, it is also

seen in the distal ileum. This agent has never been found in muscle, blood, or milk, and natural infections do not seem to spread laterally between cattle. The offspring of BSE-infected cattle have an increased risk of developing BSE, but it is not known whether this is due to vertical transmission or another mode of transmission.

Incubation period

All TSEs have incubation periods of months or years. The incubation period of BSE is more than a year and often several years. The peak incidence of disease occurs in 4 to 5 year old cattle.

Clinical signs

Bovine spongiform encephalopathy is usually insidious in onset and tends to progress slowly. The clinical signs are neurologic and once the symptoms appear, the disease is relentlessly progressive and fatal. The clinical signs of BSE may include hyperesthesia, hindlimb ataxia, pelvic swaying, hypermetria, tremors, falling, and behavioral changes such as apprehension, nervousness, and occasionally frenzy. Intense pruritus is not usually seen. Nonspecific symptoms include loss of condition, weight loss, and decreased milk production. Decreased rumination, bradycardia, and altered heart rhythms have also been reported. The disease progresses to recumbency and coma, and death occurs weeks to months later. Rare cases may develop acutely and progress rapidly within days.

Post mortem lesions

The only gross lesions found include emaciation or wasting of the carcass in some cases. The typical histopathologic lesions are confined to the central nervous system. Neuronal vacuolation and non-inflammatory spongiform changes in the gray matter are pathognomonic. Amyloid plaques are rarely seen in BSE cases. Lesions are usually but not always bilaterally symmetrical.

Morbidity and mortality

BSE is always fatal once the symptoms appear. In 1992, the annual incidence of BSE in United Kingdom cattle was 1%; however, the number of cases has been decreasing in recent years. The peak incidence in the UK occurred in January 1993 with 1,000 new cases every week.

Diagnosis

Clinical

BSE should be suspected in animals that develop a slowly progressive, fatal neurologic disease.

Differential Diagnosis

The differential diagnosis of BSE includes nervous ketosis, hypomagnesemia, listeriosis, polioencephalomalacia, rabies, brain tumor, spinal cord trauma, and lead poisoning.

Laboratory Tests

BSE is diagnosed by histopathology. A diagnosis can also be made by detecting PrPSc (a disease-specific isoform of the membrane protein PrP) in the central nervous system. Accumulations of PrPSc can be found in unfixed brain extracts by immunoblotting and in fixed brains by immunohistochemistry. The diagnosis can also be confirmed by finding characteristic fibrils of PrPSc (scrapie-associated fibrils) with electron microscopy in brain extracts. Some of

these tests can be used on frozen or autolyzed brains. BSE can be detected by transmission studies in mice. However, an incubation period of several months often makes this technique impractical for diagnosis. New commercial tests to detect BSE (PrPSc) in cattle brain samples include a modified immunoblot, a chemiluminescent ELISA test, a sandwich immunoassay, and a two-site noncompetitive immunometric procedure. Serology is not useful for diagnosis, as antibodies are not made against the BSE agent.

Samples to collect

Before collecting or sending any samples from animals with a suspected foreign animal disease, the proper authorities should be contacted. Samples should only be sent under secure conditions and to authorized laboratories to prevent the spread of the disease. A fatal human encephalopathy (vCJD) has been linked to BSE; samples should be collected and handled with all appropriate precautions.

For post-mortem examination, the whole brain, brain stem, or medulla should be extracted as soon as possible after death for histopathology. For specific PrP detection, cervical spinal cord or caudal medulla should be extracted and frozen soon after death. During epidemics of BSE, it may be possible to remove only the hindbrain via the foramen magnum for disease monitoring.

Recommended action if BSE is suspected

Notification of authorities

BSE is an exotic disease and authorities must be notified immediately of any suspicious cases. Federal Area Veterinarian in Charge (AVIC) www.aphis.usda.gov/vs/area_offices State veterinarian http://aphis.usda.gov/vs/sregs/official/html

Quarantine and disinfection

BSE does not appear to spread laterally, but once an animal is found positive the whole herd is quarantined and trace backs will occur. The prototype agent, scrapie, is highly resistant to disinfectants, heat, ultraviolet radiation, ionizing radiation, and formalin, especially if it is in tissues, dried organic material or at a very high titer. A single porous load autoclave cycle of 134-138°C for 18 minutes has been recommended for inactivation, however, this temperature range may not completely inactivate the prion protein. Infectious tissues should either be autoclaved under the same conditions or incinerated. Sodium hypochlorite and sodium hydroxide are effective chemical disinfectants; sodium hypochlorite containing 2% available chlorine or 2-N sodium hydroxide should be applied for more than 1 hour at 20°C and overnight for equipment. These recommended decontamination measures will reduce titers but may be incompletely effective if dealing with high titer material, when agent is protected within dried organic matter, or in tissue preserved in aldehyde fixatives. The prion protein may survive in tissues post-mortem after a wide range of rendering processes. Related hamster scrapie infectivity can survive interment in soil for 3 years and dry heat of 1 hour at temperatures as high as 360°C.(information obtained from OIE website at http://www.oie.int/eng/maladies/fiches/a_B115.htm) Rendering at 133^{o}C at 3 bar pressure for a minimum of 20 minutes is used in Great Britain in order to dispose of the infected carcasses. Many medical experts recommend the use of disposable instruments in neurosurgery if the risk of contacting highly infective CJD tissue is high. Equipment used for brain biopsies in the U.K. is quarantined until a diagnosis is confirmed because risk of CJD spread is too high to try and disinfect to reuse those instruments.

U.S. prevention and control prior to December 2003

The U.S. Department of Agriculture (USDA) has a number of stringent safeguards in place to prevent the spread of BSE in this country. In 1989, importation bans on live ruminants and restrictions on most ruminant products from countries where BSE had been diagnosed (including the U.K.) were initiated. These were expanded to include all European countries in December 1997. Additionally, active targeted surveillance measures for BSE have been implemented in the U.S. since 1990. Efforts focused on animals of highest risk. These include adult animals exhibiting any sign of neurological disease or distress, non-ambulatory ("downer") animals, rabies-negative cattle, as well as cattle that die on farms (added in 2002). In 2003, approximately 20,000 head of cattle were tested for BSE, which was 47 times more samples than recommended by OIE guidelines.

In August 1997, FDA initiated regulations, known as the "animal feed rule," to further enhance BSE prevention efforts. The rule prohibits the feeding of most mammalian material to ruminant animals, including cattle. The regulation exempts the following products: blood and blood byproducts, milk products, pure porcine and pure equine proteins, plate waste, tallow, gelatin and non-mammalian protein (Poultry, marine, vegetable). Additionally, it regulates the process and control system for producing feed for ruminants so it does not contain the prohibited mammalian tissue (i.e., brain, eyes, spinal cord, etc.). On December 7, 2000, the USDA prohibited importation of all rendered animal protein products, regardless of species, from any European country.

Prevention measures for the human food chain are also in place. Since 2002, FSIS has prohibited any spinal cord tissue from inclusion in products produced by advanced meat recovery (AMR) processing and labeled as "meat". Routine sampling of product was initiated by FSIS in March 2003 to ensure the regulation was followed. AMR is an industrial technology that removes muscle tissue from the bone of beef carcasses under high pressure without incorporating bone material when operated properly.

The U.S. BSE Response Plan

In 1990, the Animal and Plant Health Inspection Service (APHIS) of USDA developed an initial plan to respond to confirmation of BSE in the United States. The BSE Emergency Disease Guideline (or the BSE Red Book) includes a step-by-step plan of action to address identification of suspect animals, laboratory confirmation, epidemiologic investigation, animal and herd disposition activities, as well as communication and notification plans. The guideline was updated, revised and approved by officials at all levels of APHIS, Food Safety Inspection Service (FSIS), and USDA in 1996.

APHIS and FSIS investigators also receive comprehensive training in the detection and diagnosis of BSE. Prior to slaughter, any animal with neurological conditions is inspected by FSIS and considered suspect for BSE. The carcass is condemned and not allowed for use in the human food chain. The brain tissue is forwarded to APHIS' National Veterinary Services Laboratory (NVSL) for histopathology and immunohistochemistry. If a presumptive diagnosis of BSE is suggested, the sample is then hand carried by a NVSL pathologist to the BSE world reference laboratory in the United Kingdom for confirmation. Within 24 hours upon confirmation of a

case of BSE, the Office of International Epizooties (OIE) is notified. Notification protocols for all agencies involved in the response plan are then initiated by NVSL. The VS Area Veterinarian-in-Charge (AVIC), in cooperation with State animal health authorities, coordinates any field activities and the suspect animal's herd of origin is quarantined.

U.S. Response to First Case of BSE

On December 23, 2003, the USDA reported the first presumptive case of BSE in the U.S. It was discovered in a "downer" dairy cow in the state of Washington that had been sent to slaughter. In accordance with the U.S. BSE response plan, brain tissue was forwarded to the NVSL. Upon finding a presumptive positive result, tissue was hand delivered to the BSE world reference laboratory in Weybridge, England. Additionally, samples were forwarded to the National Animal Disease Center (NADC) and the Meat Animal Research Center for further diagnostics and DNA testing. On December 25, the UK world reference laboratory confirmed the diagnosis of BSE. Upon completion of DNA testing, the positive cow was identified as one imported from a dairy farm in Alberta, Canada.

Even though effective safeguard measures were already in place in the U.S., the Secretary of Agriculture, Ann Veneman, announced on December 30, 2003, additional safeguards being implemented due to an abundance of caution, to further strengthen protections against BSE in the U.S. These additional safeguards include the following:

1) All downer cattle presented for slaughter will be banned from the human food chain. Additionally any suspect cattle (i.e., adults with neurological conditions) will be held until BSE tests are confirmed negative;
2) Specified risk material (SRM) will also be prohibited from the human food chain. This material includes the skull, brain, trigeminal ganglia, eyes, vertebral column, spinal cord and dorsal root ganglia of cattle over 30 months of age. Additionally, the distal ileum and tonsils (which is already prohibited) from all cattle are prohibited;
3) Additional process controls were also determined for AMR systems. Prior regulations prohibited spinal cord tissue in product going into the human food chain, which is routinely verified by FSIS officials through testing of product. Regulations have now been expanded to prohibit dorsal root ganglia, skull, as well as any spinal cord tissue in processing;
4) The use of air-injection stunning of cattle at slaughter has also been prohibited immediately to reduce the potential of brain tissue being dislocated into the tissue of carcasses;
5) Additionally, a national animal identification plan (which was previously being developed) will begin immediate implementation.

The Secretary has also appointed an international panel of scientific experts to provide an objective review of the U.S. response actions to this case, as well as areas of potential improvement.

Public health aspects

Current thinking is that people who ingest BSE contaminated food products may develop variant Creutzfeldt Jakob Disease (vCJD). The incubation period for vCJD is unknown because it is a

relatively new disease, but it is likely that it is many years or decades. Therefore, a person who develops vCJD likely would have consumed an infected product or products many years earlier. In contrast to classic CJD, vCJD in the UK predominantly affects young people with 28 years as the mean age at death. The mean duration of infection is 14.1 months for vCJD. vCJD has atypical clinical features (as compared to CJD), with prominent psychiatric or sensory symptoms at the time of clinical presentation. Onset of neurological abnormalities with vCJD is delayed and includes ataxia within weeks or months. Dementia and myoclonus occur later in the illness. Affected persons generally become completely immobile and mute at the end stage of the disease. There is no known effective treatment for vCJD though there is experimental treatment taking place with quinicrine. Supportive treatment and symptomatic care are recommended. From 1995 (when the first suspected cases of vCJD occurred) to December 1, 2003, a total of 153 cases of vCJD have been reported worldwide; of these, 113 cases have occurred in the U.K. There have been no confirmed cases of vCJD originating in the United States.

For more information

World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Standards
http://www.oie.int/eng/normes/mmanual/a_summry.htm

United States Department of Agriculture Animal and Plant Health Inspection Service
http://www.aphis.usda.gov/

Canadian Food Inspection Agency
http://www.inspection.gc.ca/english/anima/heasan/disemala/disemalae.htm

Animal Health Australia. The National Animal Health Information System
http://www. aahc.com.au/nahis/disease/dislist.asp

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"Veneman annouces additional protection measures to guard against BSE." US Department of Agriculture. News Release December 30, 2003. <http://www.usda.gov/news/relaeses/2003/12/0449.html>.

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